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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,480	MACKAY, CHARLES REAY	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22,27,28,30-35 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22,27,28,30-35 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-1-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6-9, 11-13, 21, 23-26, 29, 36-39 and 41 have been canceled. Claims 1-5, 10, 1-20, 22, 27, 28, 30-35 and 40 remain pending.

Applicant's arguments filed 7-1-10 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Please do not use bold face type when amending claims.

Specification

The title of the invention has been changed to more closely reflect the fact that the claims are limited to a transgenic mouse.

Claim Rejections - 35 USC § 101

The rejection of claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. 101 because the claimed invention lacks patentable utility was previously withdrawn because agonists and antagonists of C5aR were known in the art as being used for therapy (pg 2, lines 9-21). One such known antagonist to C5aR known to treat disease was 3D53 (Monk of record, 2007; pg 436, paragraph bridging col. 1-2; col. 2, 1st full paragraph). Monk (2007) summarized treatment using 3D53 on pg 437 (Table 2), many of which were known prior to 12-24-03 (see "References" column of Table 2, which was many references published in 2003 or before). In addition, pg 62, lines 20-35, discuss a method of screening drugs using homozygous human C5aR knockin mice.

Claim Rejections - 35 USC § 112

New matter

Claims 28, 30-35, 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrase "or tissue or cells obtained therefrom" in claim 28 is new matter. Support has not been provided and none can be found.

Enablement

Claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims

Claim 1 is drawn to a transgenic mouse comprising a polynucleotide encoding a human C5aR or humanized C5aR, wherein the C5a endogenous to the mouse binds to and effects signaling of the human or humanized C5aR, and wherein the transgenic mouse is homozygous for the polynucleotide encoding a human or humanized C5aR.

Claim 15 is drawn to a method for producing a transgenic mouse for testing compounds for an effect on a phenotype associated with C5aR signaling, the method

comprising introducing into the genome of a mouse a polynucleotide construct encoding human C5aR, humanized C5aR or a fragment of human C5aR, to produce a transgenic mouse, wherein the C5a endogenous to the mouse binds to and effects signaling of the human or humanized C5aR.

Claim 28 is drawn to a method for evaluating at least one pharmacokinetic and/or pharmacodynamic effect of a candidate compound, the method comprising administering a candidate compound to a transgenic mouse according to claim 1 or isolated tissue or cells obtained therefrom, and examining at least one pharmacokinetic and/or pharmacodynamic effect of the candidate compound on the transgenic mouse or isolated tissue or cells obtained therefrom.

C5aR

C5a binds C5a receptor (C5aR) (pg 1, line 28).

Morgan (WO 95/00164) taught human C5a is one of the best described and most potent proinflammatory mediators derived from the complement system. Morgan states C5a possess multiple biologic activities that relate to host defense and may play a role in inflammatory disease processes.

Since the time of filing, Lee (Nature Biotech., Oct. 2006, Vol. 24, No. 10, pg 1279-1284) taught C5a binding C5aR facilitates leukocyte chemotaxis and release of inflammatory mediators (abstract), which is not disclosed in the instant specification. In fact in 2007, Monk (British J. Pharm., 2007, Vol. 152, pg 429-448) taught the function of C5aR was previously misunderstood and the understanding of the physiology of C5a improved by using knockout and knockin mice (pg 429, abstract).

Teachings in the specification and rejections

The specification fails to adequately teach those of skill to make the knockin mouse described in Example 1. Accordingly, the specification fails to adequately teach how to make the mouse of claim 1 or use the method of claim 15. Pg 51, lines 9-16, discusses Fig. 1, which describes the targeting construct used to make the transgenic mice in the Examples. However, the structure of the targeting construct is not readily apparent from Fig. 1. In particular, the region of "mouse-human fusion" is unclear and does not teach what area of the mouse C5aR has been replaced with human sequences or what promoter is driving the human C5aR sequences. Such information is essential to make applicants invention, and without such guidance, it would have required those of skill in the art at the time of filing undue experimentation to determine how to use heterozygous C5aR mice to screen compounds, and the claims should be limited to homozygous C5aR mice. Applicants' arguments regarding obviousness include mention of unexpected results that human C5aR would bind mouse C5a. Assuming that is true, this goes towards unpredictability of the invention, and applicants have failed to enable those of skill in the art by teaching the essential human C5aR sequences used to replace endogenous mouse C5aR sequences and the structure of the targeting vector. It is also noted that the targeting vector requires a cre-lox system which is not in the claims. If cre-lox elements are essential in the targeting vector to make the mouse, then the structure of the targeting vector must be included in the mouse claimed and include the cre-lox elements that are essential to make the mouse.

Claim 28 is drawn to evaluating a compound by administering the compound to the mouse of claim 1 (or isolated tissues or cells obtained therefrom) and examining a pharmacokinetic/pharmacodynamic effect of the compound. However, the specification fails to enable those of skill to determine how to use the mouse of claim 1 to screen drugs. The specification teaches agonists and antagonists of C5aR were known in the art as being used for therapy (pg 2, lines 9-21). One such known antagonist to C5aR known to treat disease was 3D53, which was described in 1999 by Wong (IDrugs, 1999, Vol. 2, pg 686-693) (see Monk of record, 2007; pg 436, paragraph bridging col. 1-2; col. 2, 1st full paragraph). Monk (2007) summarized treatments of disease using 3D53 on pg 437 (Table 2), many of which were known prior to 12-24-03 (see "References" column of Table 2, which was many references published in 2003 or before).

The specification teaches using the knockin mice to screen anti-inflammatory compounds (pg 7, lines 23-30; pg 59, line 23). The knockin mice were subjected to sera from a K/BxN model of rheumatoid arthritis; K/BxN mice express a transgene encoded T cell receptor (TCR) reactive to a self-peptide derived from the ubiquitously expressed glycolytic enzyme GPI, wherein the mice spontaneously develop arthritis (pg 59, lines 26-36). Serum from arthritic K/BxN mice was injected intraperitoneally into H5Rf/H5Rf knockin mice (pg 61, lines 16-21). The mice develop signs of inflammation indicating the human C5aR is expressed and the receptor is processed correctly to the G-protein signaling system (pg 61, lines 24-26; pg 62, lines 4-9). The specification states:

"The human C5aR knock-in mice were developed as a useful tool to screen anti-human

C5aR compounds for anti-inflammatory activity. To test the utility of the mice we administered both homozygous hC5aR and wild-type (control) mice an antibody specific for human C5aR (it does not bind to mouse C5aR) or a control antibody (same isotype but irrelevant specificity) in the K/BxN model and determined the effect of the antibody on inflammatory disease progression. The antibody was injected i.p. twice (200 ug per dose), one day before and one day following the first K/BxN serum injection. Mice were monitored as described above." (pg 62, lines 20-27)

Overall, it is unclear how the "homozygous hC5aR and wild-type (control) mice" are "in the K/BxN model" as described by applicants. Second, it was predetermined that the anti-human C5aR antibody targeted hC5aR and not mouse C5aR, so the controls required to identify compounds that specifically target hC5aR using the mice claimed are not described by applicants. Pg 62, lines 20-35, discuss a method of screening drugs using homozygous human C5aR knockin mice without teaching the specific steps required to do so. Applicants have left those skilled in the art with no information how to use the non-human mammals claimed to identify compounds that target human C5aR. Finally, merely observing whether a compound known to specifically target human C5aR decreases inflammation in a knockin mouse (given K/BxN sera?) as compared to a control is not an enabled use in and of itself because the compound was already known to treat disease. Therefore, using the knockin to screen anti-inflammatory compounds already known to target human C5aR is not an enabled use. As such, applicants have merely provided a starting point for further research and not provided an end point of a research effort in determining how to identify compounds of interest using the knockin claimed.

Claims 1-5, 10, 12, 14-20, 22, 27, 28, 30-35 and 40 encompass mice expressing human or humanized C5aR while still expressing their endogenous C5aR gene. The

specification and the art at the time of filing do not teach how to use a mouse expressing both human C5aR while still expressing their endogenous C5aR gene. The specification is limited to a transgenic mouse whose genome comprises a homozygous disruption in a mouse C5a receptor gene, and whose genome is homozygous for a nucleic acid sequence encoding human C5aR. Thus, it would have required those of skill in the art at the time of filing undue experimentation to determine how to use heterozygous C5aR mice to screen compounds, and the claims should be limited to homozygous C5aR mice.

Response to arguments

Applicants argue pg 50 shows the targeting locus; therefore, applicants' conclude those of skill could determine how applicants made the targeting construct. Applicants' argument is not persuasive. The sequence of the targeting locus, i.e. the C5aR gene, was known in the art at the time of filing and is not the issue. The issue is that the structure of the targeting construct made by applicants, i.e. the elements that went into the construct and their order, is not disclosed.

Applicants argue the Cre-Lox system is not essential for the invention. Applicants argue many selectable markers may be used to make transgenic mice. Applicants' arguments are not persuasive. It appears that the Cre-Lox system was used in the targeting construct made by applicants. The Cre-Lox system is employed to prevent embryonic lethality; therefore, the structure of the Cre-Lox system used by applicants is essential to prevent embryonic lethality. Use of selectable markers has nothing to do with preventing embryonic lethality. In particular, it is unclear what

promoters and control regions were used in the Cre-Lox targeting constructs. The fact that Cre-Lox systems were known in the art at the time of filing does not enable those of skill to determine the specific structure of the Cre-Lox system made by applicants because each Cre-Lox system is specific to the gene and desired tissue for expression. The specification has left all of the experimentation to those of skill in the art, which in this regard would be undue because of the infinite number of options for Cre-Lox systems and because using a Cre-Lox to prevent embryonic lethality appears to be essential to making the mouse.

Applicants argue claim 28 is enabled because pg 60, lines 11-15, teach sera from arthritic K/BxN mice was injected into homozygous C5aR and wild-type control mice. Applicants' argument is not persuasive for reasons set forth above.

Applicants argue those of skill would know how to use the mouse claimed to test compounds when the mouse is given K/BxN serum. Applicants' argument is not persuasive. Claim 28 is not limited to using a mouse given K/BxN serum. Furthermore, applicants have not explained how to perform the method and identify agents that target C5aR, i.e. what controls are required to identify agents that target C5aR? Merely looking for inflammation in the mouse does not necessarily indicate the agent is acting on the C5aR.

Applicants' response fails to address the rejection regarding using mice expressing human or humanized C5aR while still expressing their endogenous C5aR gene.

Claim Rejections - 35 USC § 103

Claims 1-5, 10, 14-20, 22, 27, 28, 30-35 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (Thrombosis and Haemostasis, 1999, Vol. 82, No. 2, pg 865-869), Roebroek (Methods in Molecular Biology, 2003, Vol. 209, 187-200), Homanics (2002, Methods in Alcohol related neuroscience research, Editor, Liu, Yuan, pg 31-61), Lester (Current Opin. Drug Discovery and Development, 2003, Vol. 6, No. 5, pg 633-639), Champtiaux (Current Drug Targets-CNS & Neurological Disorders, 2002, Vol. 1, pg 319-330), Girardi (J. Clin. Invest., Dec. 2003, Vol. 112, No. 11, pg 1644-1654) in view of Burmer (WO 02/61087-A2) and Cain (Biochemical Pharm., 2001, Vol. 61, No. 12, pg 1571-1579) and supported by Drago (Cellular and molecular life sciences, July 2003, Vol. 60, pg 1267-1280), Gu (Developmental Cell, July 2003, Vol. 5, pg 45-57), Belmont (WO 2002/059263), and Kane (WO 2003/027252).

Sato taught a knock-in mouse had an endogenous gene replaced with an exogenous gene or a mutant form of the endogenous gene (pg 866, col. 1, Gene Knock-in). Roebroek taught various strategies for making knockin mice and provided numerous references prior to applicants effective filing date that describe disrupting an endogenous mouse gene and replacing it with the human homologous cDNA (pg 188, 2.2; pg 190-191, 3.1) where the human receptor encoded by the transgene binds the mouse ligand and functions in vivo. One example of a receptor mouse known at the time of filing was Homanics who taught disrupting a mouse receptor gene and replaced with homologous human receptor cDNA. Other examples of receptor knockin mice are described by Lester and Champtiaux. Cells were isolated from the mice, and

compounds were administered to the mice for pharmacokinetic evaluation. Sato, Roebroek, Homanics, Lester, Champtiaux did not disrupt the mouse C5aR gene and replace it with human C5aR cDNA.

However, knocking out the mouse C5aR gene in a mouse was known in the art at the time of filing as described by Girardi. Furthermore, human C5aR cDNA was known in the art at the time of filing as described by Burmer (SEQ ID NO: 79). In addition, Cain taught mutated human C5aR that functioned in rat cells that "resemble mouse at these positions" (pg 1573, col. 2, section 3.2).

Thus it would have been obvious to those of ordinary skill in the art at the time the invention was made to make a humanized receptor knockin mouse as was well known in the art at the time of filing using the human C5aR cDNA of Burmer or the mutated human C5aR of Cain. Those of ordinary skill in the art at the time the invention was made would have been motivated to replace the mouse C5aR gene with human C5aR cDNA to test the functional redundancy of the gene, i.e. to test whether or not the exogenous gene can replace the function of the endogenous gene.

In addition, knockin mice having a humanized receptor were known in the art to bind the mouse ligand as exemplified by Drago (Cellular and molecular life sciences, July 2003, Vol. 60, pg 1267-1280; a leucine-to-serine point mutation in a critical residue within the second transmembrane domain of the α4 nAChR subunit (L9'S knockin); pg 1274, col. 1, 2nd partial paragraph), Gu (Developmental Cell, July 2003, Vol. 5, pg 45-57), Belmont (WO 2002/059263) and Kane (WO 2003/027252). Finally, the claims encompass mice having a point mutation in the mouse receptor that is found in the

human receptor (a humanized receptor as claimed); the claims are not limited to a mouse expressing the entire human C5aR in the absence of the mouse C5aR. Thus, those of ordinary skill in the art at the time of filing would have had a reasonable expectation of obtaining a mouse expressing a human C5aR or humanized C5aR that bound mouse C5a that effects signaling as claimed.

Response to arguments

Applicants argue those of skill would not expect the human C5aR in the transgenic claimed to be activated by mouse C5a or that it would function. Applicants point to the Declaration by Dr. Gerard which shows the homology of the extracellular domain of mouse, rat and human C5aR. Applicants' arguments and the declaration are not persuasive.

First, the specification and applicants' arguments fail to show mouse C5a "binds to and effect signaling of the human C5aR" in the transgenic mouse as claimed.

Next, the transgenic mice described by applicants did not have a normal phenotype; therefore, it is unclear mouse C5a does "bind to and effect signaling of the human C5aR".

Next, Cain taught mutated human C5aR that were made to "resemble mouse at these positions" functioned in rat cells (pg 1573, col. 2, section 3.2). Therefore, despite the lack of 100% homology of mouse and human C5aR, those of ordinary skill would have known how to make a mutated human C5aR that functioned in murine cells and had a reasonable expectation of mouse C5a binding human C5aR as evidenced by Cain.

It is noted that the claims encompass using any "humanized C5aR" which encompasses any mutation that makes the mouse C5aR more like human C5aR (including the mutation described by Cain or any single amino acid substitution that make the mouse C5aR more like human C5aR). The claims are not limited to replacing the entire mouse gene with the entire human gene.

It is also noted that applicants' arguments regarding Cain indicate a difference in binding of known agonists to mouse and human C5aR; however, variation in binding of agonists to mouse and human C5aR fails to indicate mouse C5a will not bind and effect signaling of human C5aR.

Applicants argue Drago did not teach humanized receptor bound mouse ligand. Applicants' argument is not persuasive. Pg 1274, col. 1, 2nd partial paragraph, shows a leucine-to-serine point mutation in a critical residue within the second transmembrane domain of the α4 nAChR subunit (L9'S knockin) effects signaling which implies binding of ligand to the receptor.

Applicants argue Gu did not teach humanized receptor bound any of the multiple possible mouse ligands. Applicants' argument is not persuasive. Gu taught the humanized receptor effected signaling which implies binding of at least one of the multiple ligands to the receptor.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Kedmi, Society for Neurosci. Abstract Viewer and Itinerary Planner, 2003, Vol. 2003, pp Abstract No. 533.12

Wang, Blood, 2002, Vol. 11, Nol. 11, Abstract 2681

Rozmahel (Human Mol. Genetics, 1997, Vol. 6, Nol. 7, pg 1153-1162)

Woodruff (Arthritis and Rheumatism, Sept. 2002, Vol. 46, No. 9, pg 2476-2485).

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday through Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner